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AGILENT TECHNOLOGIES, INC.
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EXAMINER

MUMMERT, STEPHANIE KANE

ART UNIT	PAPER NUMBER
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1637

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/052,926

Applicant(s)

SAMPSON, JEFFREY R.

Examiner

STEPHANIE K. MUMMERT

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period **will** apply and **will** expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply **will**, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 30 November 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-35, 67-101 and 144-149 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-35, 67-101 and 144-149 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

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DETAILED ACTION

Applicant's amendment filed on November 30, 2007 is acknowledged and has been entered. Claims 1 and 67 have been amended. Claims 36-66 and 102-143 have been canceled. Claims 1-35, 67-101 and 144-149 are pending.

Claims 1-35, 67-101 and 144-149 are discussed in this Office action.

Applicant's arguments, see p. 9-10, filed November 30, 2007, with respect to the rejection of claims 1-35, 67-101 and 144-149 have been fully considered and are persuasive. The ground of rejection has been withdrawn.

All of the remaining amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-35, 67-101 and 144-149 are pending and will be examined.

This action is made FINAL as necessitated by amendment.

New Grounds of Rejection necessitated by amendment

Claim Interpretation

While the term ‘modified nucleotide’ is addressed in the specification, the definition does not provide an explicit definition of the term. Instead, the term is defined in general terms such as “Modified bases (excluding A, T, G, C, and U) include for example, bases having a structure derived from purine or pyrimidine (i.e. base analogs). For example without limitation, a modified adenine may have a structure comprising a purine with a nitrogen atom covalently bonded to C6 of the purine ring as numbered by conventional nomenclature known in the art” (paragraph 17 of PgPub). The specification also teaches that the modified nucleotide has “a reduced ability to form base pairs with complementary modified or unmodified nucleic acids” (paragraph 10 of PgPub). Therefore, the term is being interpreted as reading on art directed to the inclusion of any kind of nucleotide that reduces hydrogen bonding or base pairing between ‘natural’ and modified oligonucleotide sequences.

The term ‘at least one repeat of a nucleic acid’ is not provided with an explicit definition in the specification. Instead, the term is defined in general terms such as “the present invention generates nucleic acid polymers for nanopore sequencing having multiple tandem repeats” (paragraph 8 of PgPub). Therefore, as the term requires at least one repeat and not tandem repeats, and without an explicit definition, the term is being interpreted as reading on art directed to any repeated nucleotide sequences in the nucleic acid.

Claim Rejections - 35 USC § 103

1. Claims 1-5, 8-34, 67-71, 74-100 and 144-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) and Kutuyavin et al. (US Patent 5,912,340; June 1999). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

With regard to claim 1 and 67, Church teaches a method of sequencing a nucleic acid molecule comprising steps of:
providing two separate, adjacent pools of a medium and an interface between the two pools, the interface having a channel so dimensioned as to allow sequential nucleotide-by-nucleotide passage from one pool to the other pool of only one nucleic acid molecule at a time (Figure 1, where the method is depicted schematically; col. 1, line 35, col. 2, line 8, where two adjacent pools of medium are provided with an interface which is capable of interacting with individual monomer residues of a single polymer); producing a nucleic acid molecule with at least one repeat of a nucleotide sequence to be determined (col. 11, lines 38-41, where nucleic acids with repeating identical bases are resolved, where 'punctuation' in the conductance is registered through a distinct/higher level of conductance between bases); placing the nucleic acid molecule in one of the two pools; and taking measurements as each of the nucleotides of the nucleic acid molecule passes through the channel so as to determine the sequence of the nucleic acid molecule (col. 1, line 35 to col. 2, line 8, where a single polymer is present in one of the two pools and interface dependent measurements are taken leading to characterization of polymers in the mixture and the method can be used to determine their sequence).

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With regard to claim 2 and 68, Church teaches an embodiment of claim 1 and 67, wherein the nucleic acid is single- stranded (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA).

With regard to claim 3 and 69, Church teaches an embodiment of claim 2 and 68, wherein the nucleic acid is single-stranded DNA (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA).

With regard to claim 4 and 70, Church teaches an embodiment of claim 2 and 68, wherein the nucleic acid is single-stranded RNA (col. 7, lines 31-34; col. 10, lines 18-24, where the nucleic acid comprises single or double-stranded DNA; col. 7, lines 55-60, where the polymer can comprise RNA).

With regard to claim 8 and 78, Church teaches an embodiment of claim 1 and 67, wherein the medium is electrically conductive (col. 2, lines 35-37, where the pools include electrically conductive medium, either the same or different composition; col. 2, lines 59-64, where the electrically conductive medium can be any medium, including an aqueous solution).

With regard to claim 9, 20, 28, 79, 90, 98, Church teaches an embodiment of claim 8, 19, 27, 78, 89, 97, wherein the medium is an aqueous solution (col. 2, lines 9-13, where the pools are liquids, usually aqueous solutions; col. 2, lines 59-64, where the conducting medium is any medium and preferably an aqueous solution).

With regard to claim 10, 14, 21, 23, 80, 84, 91, 93, Church teaches an embodiment of claim 8, 9, 20, 22, 78, 79, 90, 92, further comprising applying a voltage across the interface (col. 2, line 64 to col. 3, line 3, where voltage is applied across the barrier between the pools; col. 4, lines 57-67, where the passage is preferably voltage sensitive or voltage-gated).

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With regard to claim 11, 15, 22, 24, 29, 30, 81, 85, 92, 94, 99, Church teaches an embodiment of claim 10, 14, 21, 23, 27, 28, 81, 84, 91, 93, 98, wherein ionic flow between the two pools is measured (col. 2, lines 35-47, where the conductive pools are separated by an impermeable barrier with an ion-permeable passage, an electrical potential between the two pools is established and ionic current is allowed to flow across the passage).

With regard to claim 12, 16, 25, 82, 86, 95, 100, Church teaches an embodiment of claim 11, 15, 24, 81, 85, 94, 97, wherein the duration of ionic flow blockage is measured (col. 4, lines 31-35, the characteristics of the polymer can be identified by amplitude and duration of individual conductance changes across the passage).

With regard to claim 13, 17, 26, 83, 87, 96, Church teaches an embodiment of claim 11, 15, 25, 81, 84, 94, wherein the amplitude of ionic flow blockage is measured (col. 4, lines 31-35, the characteristics of the polymer can be identified by amplitude and duration of individual conductance changes across the passage).

With regard to claim 18 and 88, Church teaches an embodiment of claim 1 and 67, wherein the nucleic acid polymer interacts with an inner surface of the channel (col. 6, lines 59-65, where the polymer passage through the interface results in monomer interactions with the interface that are sufficient to identify the monomers or the characteristics of the polymer; col. 20, lines 24-29, where “short duration blockades represent polymers that interact with the channel (e.g., loops of polymer that come to lie on the channel aperture)”).

With regard to claim 19 and 89, Church teaches an embodiment of claim 18 and 88, wherein the medium is electrically conductive (col. 2, lines 35-37, where the pools include

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electrically conductive medium, either the same or different composition; col. 2, lines 59-64, where the electrically conductive medium can be any medium, including an aqueous solution).

With regard to claim 27 and 97, Church teaches an embodiment of claim 1 and 67, further comprising providing a polymerase or exonuclease in one of the two pools, wherein the polymerase or exonuclease draws the nucleic acid polymer through the channel (col. 7, lines 27-31, where a polymerase is fused with the pore to pull the nucleic acid through the channel; col. 12, lines 65-67).

Regarding claim 1 and 67, Church does not teach the steps wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule.

With regard to claims 1 and 67, Morgan teaches a method comprising producing a nucleic acid molecule wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and “probably resulted from loss of intermolecular base pairing”).

With regard to claim 5 and 71, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid is an unstructured nucleic acid (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and “probably resulted from loss of intermolecular base pairing”).

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With regard to claim 32 and 75, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains modified guanosine and modified cytosine which are not able to form base pairs, wherein the modified guanosine is capable of forming a base pair with unmodified cytosine, and wherein the modified cytosine is capable of forming a base pair with unmodified guanosine (p. 5965, col. 1, where the lower stability of I-C as compared to G-C base pairs are discussed. In I-C base pairs there are 2 hydrogen bonds, while in G-C base pairs there are 3 hydrogen bonds present, however base pairing does occur, it is less stable).

With regard to claim 33 and 76, Morgan teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-aminoadenosine, 2-thiothymidine, inosine, and pyrrolopyrimidine (Abstract, where substitution of inosine for guanosine resulted in absence of G-C base pairs and loss of ordered secondary structure; p. 5962, col. 2, where I-substituted transcripts migrated more slowly than transcripts with normal G residues and “probably resulted from loss of intermolecular base pairing”).

Neither Church or Morgan teach the inclusion of a modified adenosine or thymine. Kutayavin teaches modified bases that form less stable hydrogen bonds, which decreases melting temperature (Abstract).

With regard to claim 1, Kutayavin teaches at least two different complementary base pair analogues, wherein the at least two different complementary base pair analogs reduce secondary structure in the nucleic acid molecule (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

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With regard to claims 31 and 74, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains modified adenosine and modified thymine which are not able to form base pairs, wherein the modified adenosine is capable of forming a base pair with unmodified thymine, and wherein the modified thymine is capable of forming a base pair with unmodified adenosine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claim 34 and 77, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-aminoadenosine, and 2-thiothymidine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine; Abstract, where it is noted that "the ODNs include modified bases of such nature that the modified base forms a stable hydrogen bonded base with the natural partner base, but does not form a stable hydrogen bonded base pair with the modified primer" and notes "due to the lack of stable hydrogen bonding with each other, the matched pair of oligonucleotides have a melting temperature" which is 40oC or less).

With regard to claim 144 and 146, Kutyavin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains a modified thymine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment

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comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

With regard to claim 145 and 147, Kutayin teaches an embodiment of claim 1 and 67, wherein the nucleic acid molecule contains 2-thiothymidine (col. 5, lines 37-61, where the general structure of the preferred A analog, A' is described, wherein a preferred embodiment comprises 2-aminoadenine; col. 6, line 56 to col. 7, line 10, where the general structure of the preferred T is described and wherein a preferred embodiment comprises 2-thiothymine).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied and incorporated the modified nucleotides of Morgan to the practice of sequencing of nucleic acids as taught by Church to arrive at the claimed invention with a reasonable expectation for success. Church teaches the inclusion of a variety of modified nucleotides, but does not teach the specific inclusion of modified analogues to affect secondary structure of templates for sequencing. Morgan teaches a method that incorporates inosine residues in place of guanosine residues in transcripts and examines the effect on secondary structure, binding and elongation. Morgan finds that "the apparent molecular weights of the I-substituted products were altered as a consequence of the absence of G-C base pairs and accompanying loss of ordered structure" (Abstract). Therefore, the method of sequencing as taught by Church is known as stated above. Church does not teach the inclusion of modified nucleotides to affect secondary structure. Morgan teaches the substitution of guanosine with inosine and results in a change in secondary structure of the nucleic acid. Therefore, considering the teachings of Morgan and Church, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the secondary structure of template nucleic acid molecules prior to

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passing these molecules through a pore for establishing sequence identity using the known technique taught by Morgan to yield a predictable result.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of modified bases by Church in view of Morgan to replace adenine and thymine in the nucleic acids of the invention to include the 2-aminoadenine and 2-thiothymine of Kutyavin to arrive at the claimed invention with a reasonable expectation for success. As taught by Kutyavin, “complementary positions in both SBC ODNs are modified into a matched pair of SBC ODNs of the present invention so that the pair of the matched set does not form a stable hybrid; in other words under physiological conditions it has a melting temperature of 40oC or less” (col. 4, lines 39-52). Furthermore, Kutyavin also teaches, “the general concept of double stranded DNA and of secondary structure in mRNA and ribosomal RNA is covered by the term ‘duplex nucleic acid’” (col. 4, lines 62-64). Kutyavin also states “a matched pair of SBC ODNs is able to sequence specifically invade the secondary structure of these duplex ribonucleic acids” (col. 25, lines 23-27). While neither Church or Morgan teaches the inclusion of analogues for A and T, Kutyavin teaches analogues for each nucleotide monomer and the reduction in hydrogen bonding stability. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated these additional analogues and reduction in binding strength associated with both analogues would result in a reduction in secondary structure, to arrive at the claimed invention with a reasonable expectation for success.

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2. Claims 6-7, 72-73 and 148-149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) and Kutuyavin et al. (US Patent 5,912,340; June 1999) as applied to claims 1-5, 8-34, 67-71, 74-100 and 144-147 above, and further in view of Lizardi et al. (US Patent, 6,632,609; October 2003). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-5, 8-34, 67-71, 74-100 and 144-147. Neither Church or Morgan teach that the nucleic acid is produced using a circular template. Lizardi teaches the synthesis and amplification of circular nucleic acid templates (Abstract).

With regard to claim 6 and 73, Lizardi teaches an embodiment of claim 1, wherein the nucleic acid is enzymatically produced using circular template that is single-stranded or double-stranded (Figures 1-4, where the open circle probe is single stranded and is ligated to form a circular template on the specific target nucleic acid and is therefore enzymatically produced).

With regard to claim 7 and 72, Lizardi teaches an embodiment of claim 6, wherein the circular template is single stranded (Figures 1-4, where the open circle probe is single stranded and is ligated to form a circular template on the specific target nucleic acid and is therefore enzymatically produced).

With regard to claim 148 and 149, Lizardi teaches an embodiment of claim 1 and 67, wherein said producing comprises contacting a circular template with a primer, a polymerase, nucleotides and modified nucleotides under rolling circle amplification conditions sufficient to

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produce said nucleic acid (col. 3, lines 1-32, where the amplification comprises these components; see also Figures 3 and 4, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of circular template production of Lizardi to the method of sequencing taught by Church to arrive at the claimed invention with a reasonable expectation for success. Church in view of Morgan teach sequence analysis of nucleic acids comprising modified nucleotides. However, neither Church or Morgan teach that the template comprises a circular template. Lizardi teaches “The DNA ligation operation circularizes a specially designed nucleic acid probe molecule. This step is dependent on hybridization of the probe to a target sequence and forms circular probe molecules in proportion to the amount of target sequence present in a sample” (col. 3, lines 10-14). Therefore, considering the circular templates taught by Lizardi, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the circular templates taught by Lizardi and this incorporation would have provided a predictable outcome with a reasonable expectation for success.

5. Claims 35 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Church et al. (US Patent 5,795,782; August 1998) in view of Morgan et al. (Biochemistry 1980, vol. 19, no. 26, p. 5960-5966) and Kutuyavin et al. (US Patent 5,912,340; June 1999) as applied to claims 1-5, 8-34, 67-71, 74-100 and 144-147 above, and further in view of Thorp et al. (US Patent 5,871,918; February 1999). Church teaches a method of sequencing a nucleic acid by measuring changes across an interface between two pools of media (Abstract).

Church in view of Morgan teach all of the limitations of claims 1-5, 8-34, 67-71, 74-100 and 144-147. Neither Church or Morgan teach the analysis of nucleic acids by electron tunneling.

With regard to claim 35 and 101, Thorp teaches an embodiment of claim 1 and 67, further comprising analyzing the nucleic acid molecules by electron tunneling (col. 9, line 18 to col. 10, lines 42, where in specific embodiments, the nucleic acid molecules are analyzed by electron tunneling).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the method of sequencing of Church to include the technique of electron tunneling detection of nucleic acid molecules as taught by Thorp to arrive at the claimed invention with a reasonable expectation for success. Church in view of Morgan teach the sequencing of nucleic acids, however neither teach the application of electron tunneling to the analysis of nucleic acid molecules. Thorp teaches the application of electron tunneling and notes that “correlation between the tunneling distance and the specific base paired with the preselected base is therefore established” (col. 10, lines 9-11). Therefore, as Thorp teaches that electron tunneling may be used to analyze nucleic acids, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the method of sequencing of Church to include the technique of electron tunneling detection of nucleic acid molecules as taught by Thorp to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 1-35, 67-101 and 144-149 have been considered but are moot in view of the new ground(s) of rejection. However, insofar as the arguments apply to the new grounds of rejection the arguments will be considered.

Applicant's arguments filed November 30, 2007 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims 31, 34, 74, 77 and 144-147 as being unpatentable over Church, Morgan and Kutyavin. Applicant asserts "Kutyavin only discloses that 'the matched pair of oligonucleotides in accordance with the present invention do not form substantially stable hydrogen bonded hybrids with one another, as manifested in melting temperature'" and goes on to state "nowhere does Kutyavin disclose or suggest the element that the modified nucleotides reduce secondary structure" (p. 12-13 of remarks).

These arguments are not persuasive. While Kutyavin may not explicitly state that the inclusion of these modified oligonucleotides reduce secondary structure, Kutyavin instead teaches as noted in the updated art rejection and motivation statement, that the inclusion of the modified nucleotides do not form a stable hybrid and that this lack of stability results in a reduced melting temperature. Kutyavin also teaches that double-stranded DNA, and mRNA or ribosomal RNA with secondary structure comprise duplex DNA. A duplex is formed as a hybrid between two nucleic acids. If the inclusion of the modified base pairs results in decreased hybrid formation, a reduction in secondary structure, which manifests as duplex formation within an mRNA or RNA, would also necessarily occur. Finally, Kutyavin also states "a matched pair of

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SBC ODNs is able to sequence specifically invade the secondary structure of these duplex ribonucleic acids” (col. 25, lines 23-27), and therefore, given a broad interpretation of the term “reduces secondary structure” in the claim as amended, the inclusion of these modified nucleotides in probes reduces secondary structure in the samples to which these probes are applied. The rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephanie K. Mummert
Patent Examiner
Art Unit 1637

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